Please replace the paragraph beginning at page 47, line ~~14~~ 21, which starts with "In the GFP gene targeting system", with the following amended paragraph:

AC 6/5/06

In the GFP gene targeting system the introduction of a DSB stimulated GT by >2000-fold and the absolute rate of gene targeting reached 3-5% when conditions were optimized. Such a system, however, depended on the prior introduction of a Sce site into the target gene and therefore can not be used for endogenous genes. To stimulate gene targeting at endogenous genes, a method to create sequence specific DSBs in those genes needs to be developed. Chimeric nucleases have such potential (Chandrasegaran et al., 1999, Biol Chem, 380:841-8). Chimeric nucleases--fusions between zinc finger binding DNA binding domains and the endonuclease domain of the FokI restriction enzyme ("Fn")--can site-specifically cleave naked DNA *in vitro* (Chandrasegaran et al., 1999, Biol Chem, 380:841-8), extra-chromosomal DNA in Xenopus oocytes (Bibikova et al., 2001, Mol Cell Biol, 21:289-97) and chromosomal DNA in Drosophila (Bibikova, et al., 2002, Genetics, 161:1169-75). Applicants decided to try to extend this methodology to stimulate gene targeting in human somatic cells (Figure 3). Figure 3A shows the structure of the expression plasmids and target sites for the chimeric nuclease experiments. Applicants designed three different chimeric nucleases, each driven by the CMV promoter and containing a nuclear localization signal at their amino-termini (Figure 3A). In two constructs (CMV-QQR-L18-Fn and CMV-QQR-L0-Fn) the DNA binding specificity was conferred by the artificial QQR three zinc finger domain that binds with nanomolar affinity to the sequence 5' GGGGAAGAA 3' (SEQ ID NO: 8) (Shi et al., 1995, Science, 268:282-284). These two constructs differed in the length of the amino acid linker between the zinc fingers and the Fn domain. The amino acid linker was 18 amino acids in CMV-QQR-L18-Fn while in CMV-QQR-L0-Fn there was no amino acid linker. CMV-ZIF-L3-Fn fused the three zinc fingers from Zif268 to the Fn domain with a 3 amino acid linker between the two domains. The Zif268 zinc finger domain recognizes the sequence 5' GCGTGGGCG 3' (SEQ ID NO: 9) with sub-nanomolar affinity (Elrod-Erickson et al., 1999, J Biol Chem, 274:19281-5). Applicants constructed three cell lines (293/QQR8, 293/QQR6, 293/QQRZIF6) with corresponding gene targets (QQR8, QQR6, and QQRZIF6). QQR8 and QQR6 have inverted repeats of the QQR binding site inserted next to the Sce recognition site (Figure 3A). QQR8 and QQR6 differed in that the repeats are separated by 8 bp in QQR8 and 6 bp in QQR6. Prior work has shown that purified QQR-Fn protein without an amino acid linker (equivalent to CMV-QQR-L0-Fn) cuts